-----Original Message-----
From: Edwards, Neil [mailto:Neil.Edwards@parexel.com]
Sent: Sunday, May 09, 2004 2:58 AM
Subject: RE: Redaction of Confidential commercial information from S. boul ardi i TEA

Dear Michael,

Thank you for your email.

I confirm that the sections of the TEA that we would like to be redacted by page number are as follows:

1. Original TEA
   All marketing information concerning the sales, ie: pages 19 to 26 and attachments 3 and 4, pages 120 to 142.

2. Addendum to TEA dated April 2004
   pages 5 to 9.

2- Table on OTC sales

I attach the table that we would wish you to include within the TEA:

Region	**Estimated OTC sales (million dosage units)**
Africa (5 countries)	40
Asia (2 countries)	17
Europe (7 countries)	1,103
TOTAL (13 countries)	1,160

Please do not hesitate to contact me should you have any further questions.

Thank you and regards,

Neil.

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PAREXEL

Re: Time and Extent Application
Central Document Room
U.S. Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville MD 20852
U.S.A.

For Attention of:
Dr. Laura Shay
Division of Over-the-Counter Drug Products

14 January 2004

Dear Dr Shay,

Re: Time and Extent Application (TEA) for *Saccharomyces boulardii.*

Please find enclosed on behalf of Laboratoires BIOCODEX a Time and Extent Application (TEA) for *Saccharomyces boulardii* (*S. boulardii*).

It is proposed that *S. boulardii* will be marketed for the symptomatic treatment of diarrhea under a revision of the current Tentative Final Monograph on Antidiarrheal Products for Over the Counter Use. To date *S. boulardii* has not been approved as a drug in the U.S.A.

S. boulardii, manufactured by BIOCODEX, is available for the treatment and/or prophylaxis of diarrhea of various etiologies in over 50 countries worldwide. The condition has been marketed in compliance with national legislation that is equivalent to OTC availability in seven European countries (Belgium, France, Germany, Italy, Portugal, Spain and Switzerland).

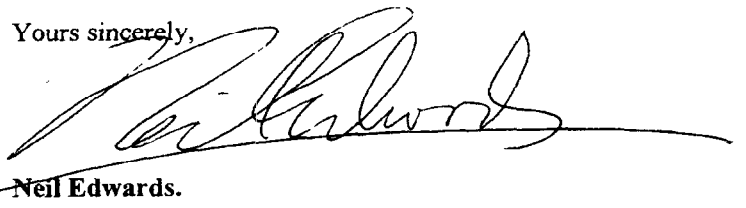
These countries have experienced more than 10 years marketing of the drug on a large scale of OTC sales and with a great number of patients exposed to the drug. It is this significant OTC use that forms the basis of the enclosed TEA.

In the event that you should have any questions arising from your review of the enclosed TEA for *S. boulardii* please do not hesitate to contact Neil Edwards, contact details are as follows:

Neil Edwards
tele: 44 (0)1895 614009
fax: 44 (0)1895 614375
email: neil.edwards@parexel.com

Thank you in advance for your consideration of the enclosed TEA.

Yours sincerely,



Neil Edwards.
Associate Director.
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On behalf of Laboratoires BIOCODEX

Enc.

CC: Dr Jean Vincent (Laboratoires BIOCODEX).

Florastor (*Saccharomyces boulardii*) :

Time and Extent Application (TEA)

Prepared by :
Dr Jean Vincent
Head of Regulatory Affairs
Laboratoires BIOCODEX
19, rue Barbès
92126
Montrouge
Cedex
France

Date : **December 2003**

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1. BASIC INFORMATION

1.1 THE CONDITION PROPOSED FOR INCLUSION IN THE OTC MONOGRAPH SYSTEM

1.1.1 Description of the Drug Substance

The active substance is the yeast, *Saccharomyces boulardii* (*S. boulardii*) in a lyophilized form.

1.1.2 Pharmacological Class

Probiotic/ biotherapeutic anti-diarrheal agent.

ATC Code : A07FA02

1.1.3 Intended OTC Use

Saccharomyces boulardii is indicated for the symptomatic treatment of diarrhea.

1.1.4 OTC Dosage Strength and Dosage Form

Capsule containing 250mg *S. boulardii*.

1.1.5 Route of Administration and Directions for Use

Route of administration : oral

Directions for use :
Adults and children 1 to 2 capsules per day. Capsules should be taken in the morning and / or in the evening.

Treatment should be continued until the symptoms of diarrhea have resolved. If no improvement is seen within two days, consult your doctor.

For young children the contents of the capsule should be mixed with a glass of water.

Children under 3 years of age: ask a doctor.

1.1.6 Applicable existing OTC Monograph Under Which the Condition would be Marketed.

Antidiarrheal Drug Products for Over-the-Counter Human Use; Tentative Final Monograph.

1.2 DETAILED DESCRIPTION OF DRUG SUBSTANCE.

1.2.1 Name of Active Substance and Proper Identification.

The active substance is the yeast, *Saccharomyces boulardii* (*S. boulardii*), in lyophilized form.

The strain is registered with the following references:

- American Type Culture Collection (ATCC), reference ATCC 74012
- Institut Pasteur de Paris, reference I.745
- Centraalbureau voor Schimmelcultures, reference CBS 5926

1.2.2 Information on the Supplier/ Manufacturer

Name and address of supplier/ manufacturing source:
Laboratoires BIOCODEX
1 avenue Blaise Pascal
60000 BEAUVAIS – FRANCE

Manufacture of lyophilized *S. boulardii* is carried out by Laboratoires BIOCODEX in compliance with current Good Manufacturing Practice.

1.2.3 Qualitative Description

Name

Saccharomyces boulardii (*S. boulardii*), in lyophilized form.

Appearance

Light brown powder with characteristic odor.
On microscopic examination *S. boulardii* presents as ovoid cells. Terminal and sub-terminal buds are frequently observed.

Properties/ Taxonomy

Culture characteristics (incubation at 30°C for 48 to 72 hours) :

Culture in Sabouraud agar with chloramphenicol : typical colonies are round, white and have a creamy appearance. They frequently show raised and slightly wrinkled central part.

Culture on Sabouraud agar medium with tetrazolium : *S. boulardii* reduces tetrazolium yielding pink to violet red colonies.

Culture on Sabouraud agar medium with actidione : *S boulardii* does not grow.

Study of assimilation of sugars and other carbohydrate products :

Differential properties of yeast evaluated by an auxanogram using API 20 C Aux Kit. The auxanographic code of *S. boulardii* is :

2 or 6	0	0	0	0	3 or 7	2

Sporulation

S. boulardii is required not to form asci even on an appropriate medium (sodium acetate, dextrose, yeast extract, agar, purified water).

1.2.4 Type of Manufacturing Process and method of purification

Lyophilised *S. boulardii* is manufactured from a stock strain by serially culturing in appropriate media and in increasingly large containers so as to obtain a pure yeast culture. Following culture, the yeast is concentrated by centrifugation and then freeze-dried after addition of lactose.

1.2.5 Quantitative Description

- Viability : $\geq 18 \times 10^9$ viable yeast cells (cfu) per g of active substance (lyophilised S. boulardii)
- Water contents must be less than 1%.

The release specifications for *S. boulardii* are as follows :

***Saccharomyces boulardii*, in lyophilised form : Specifications and routine tests**

Test	Requirement
Characteristics	Light-brown powder with characteristic odor
Identification	
- Microscopic examination	Ovoid yeast cells with no other microorganism. Frequent terminal or sub-terminal buds.
- Study of the assimilation of sugars and other carbohydrate products (API 20 C Aux)	2 or 6 | 0 | 0 | 0 | 0 | 3 or 7 | 2
- Sporulation	No ascus
Tests	
- Water content	≤ 1 %
- Viability determination	≥ 18 x 10^9/g
- Sulphated ash	≤ 7 %
- Control of microbial contamination	
• Total viable aerobic microorganisms	
⇨ Bacteria	≤ 100 CFU/g
⇨ Molds and other yeasts	none/g
• Specified microorganisms	
⇨ *Enterobacteria* and certain other Gram-negative bacteria	none/g
⇨ *Escherichia coli*	none/g
⇨ *Salmonella*	none/10g
⇨ *Pseudomonas aeruginosa*	none/g
⇨ *Staphylococcus aureus*	none/g

1.3 Analytical Test Methods

The test method used for conducting the test as detailed within the specification above are as follows :

1.3.1 Visual / organoleptic examination

Light-brown powder with characteristic odor

1.3.2 Identification

a - Microscopic examination

Suspend a little powder in water. Examine the suspension between slide and cover slip under the microscope. Only ovoid yeasts are observed. No other microorganism is present. (A phase-contrast microscope enhances observation).

Saccharomyces boulardii presents as round or oval cells of width 4 to 6 µm and length 6 to 13 µm. Terminal or sub-terminal buds are frequently observed.

b - Study of the assimilation of sugars and other carbohydrate products

This differential property of yeasts is evaluated by an auxanogram using an API 20 C Aux kit.
Transfer 3 or 4 drops of yeast suspension of absorbance between 0.20 and 0.25 at 530 nm to an ampoule of API 20 C Aux medium.
Carefully blend the contents of the ampoule. Fill the wells, using a Pasteur pipette, as per the API system instructions.
Allow to incubate at 30°C for 48 to 72 hours, then observe each well.
Well 0 is the negative control for assimilation.

The wells showing greater turbidity than the control are considered positive.
Assign a score as per the API coding system to each well so as to obtain the auxanographic code for the yeast:

2 or 6	0	0	0	0	3 or 7	2

c - Sporulation

Inoculate one or several tubes of sporulation medium with sodium acetate with yeast suspension, in streaks.

- *Sporulation medium with sodium acetate* :

Sodium acetate	10.0 g
Dextrose	1.0 g
Yeast extract	2.5 g
Agar	20.0 g
Purified water .....qs	1000 mL

Sterilize in an autoclave at 110°C for 20 minutes.

Incubate at room temperature for at least 4 days.

- *Staining :*

From a tube of medium with sodium acetate, prepare a smear on a microscope slide.

Fix with heat. Stain the slide with malachite green solution:

Malachite green solution	: Malachite green		5 g
	Purified water	qs	100 mL

Heat for about 3 minutes until white fumes are given off.
Discard the stain and rinse under running water for 30 seconds.
Overstain with safranin solution for 30 seconds:

Safranin solution	: Safranin		0.5 g
	Purified water	qs	100 mL

Rinse under running water and dry.

- *Observation*

The yeasts are required to remain pink. In some cells, a greenish spot may be observed. The spot is not to be considered an ascus.

- *Conclusion*

Saccharomyces boulardii does not produce asci.

1.3.3 Tests

a - Water content

The determination of water content with potentiometric end-point detection is conducted as per the European Pharmacopoeia, current Edition (2.5.12. Method A) using a potentiometric titrator such as a METHROM 716 DMS Titrino fitted with a double platinum electrode and commercial reagents of the Hydranal® range.

Potentiometric titrator settings :

- end point : 250 mV.
- regulation field : 200 mV.
- maximum titrant run-in rate : 5 mL/min.
- minimum titrant run-in rate : 25 µL/min.
- stop criteria (time) : 6 min.
- titration direction : negative.
- electrode polarization : 25 µA.
- temperature : 25°C.

The solvent used consists of :

Methanol	600 mL
Formamide	400 mL
Hydranal® solvent	50 mL

Hydranal® solvent ensures enhanced assay reproducibility.

After having tared a tube with an aluminum cap, dried in an oven at 105°C and stored in a desiccator, transfer a test sample (TS), accurately weighed, of about 3 g of lyophilized *Saccharomyces boulardii* to the tube.

20 mL of solvent are automatically added at the time of assay and under protection from the outside air.

To assay the water in the test sample, the potentiometric titrator with a double platinum electrode adds, by serial run-in, Hydranal® titrant reagent (pre-standardized using Hydranal® Standard 5$^{\leftarrow}$) to the end point and over 6 minutes.

A blank titration is conducted by determining the water content on 3 empty tubes stored under the same conditions as the assay tube and filled with the same reagents. The blank is determined at the start of a day.

$(V_{TS} - Vb) \times t$ = mg of water in the sample.

Where :

V_{TS} = volume of titrant run in for the test sample
Vb = volume of titrant run in for the blank
t = titer of the titrant (Hydranal®)

then : $\dfrac{\text{mg of water} \times 100}{TS \times 1000}$ = % water in the sample.

$\leftarrow$: contains 5.00 ± 0.02 mg of water per mL.

Standard : the water content of lyophilized *Saccharomyces boulardii* is required to be less than or equal to 1%.

b - Viability determination

- *Principle of the determination*

From a lyophilized *Saccharomyces boulardii* test sample, prepare a uniform stock suspension in isotonic medium. Serially dilute the stock suspension 1:10 in normal saline. Withdraw 1 mL of the 7th dilution. Transfer the sample to a sterile Petri dish. Plate with molten Sabouraud agar with chloramphenicol. Mix. Allow to cool. After

incubation, count the number of included and superficial colonies. Calculate the number of viable yeast cells contained in the sample under test.

- *Media*

Suspension liquid :

Sodium chloride		0.50 g
Chloramphenicol		0.02 g
Distilled water	qs	100 mL

Dissolve the sodium chloride and chloramphenicol in distilled water. Autoclave at 121°C for 15 minutes.

Normal saline :

Sodium chloride		0.90 g
Distilled water	qs	100 mL

Dissolve the sodium chloride in purified water. Autoclave at 121°C for 15 minutes.

Culture medium (medium 3) :

Medium 3 - Sabouraud agar medium with chloramphenicol :

Peptones (meat and casein)		*10.0 g*
Glucose monohydrate		*40.0 g*
Chloramphenicol		*0.25 g*
Agar		*15.0 g*
Purified water	*qs*	*1000 mL*

Dissolve the peptones, glucose and chloramphenicol.
Adjust the pH so that after sterilization it is 5.6 ± 0.2. Sterilize by heating in an autoclave at 121°C for 15 minutes. Immediately before use, add 0.5 mL of 0.4% actidione solution as a sterile solution.

- *Procedure*

Preparation of the stock solution

Accurately weigh a test sample, TS, of about 0.565 g of lyophilized *Saccharomyces boulardii*. Add 19.5 mL of suspension liquid (cf. composition above) at room temperature.
Add a sterile bar magnet. Stir magnetically at intermediate speed using an electromagnetic stirrer for 10 minutes immediately before diluting 1:10.

Preparation of the 1:10 dilutions

Immediately before conducting the 1:10 dilutions, transfer 9 mL of sterile normal saline at room temperature to a set of 7 test tubes.
Maintain the tubes at room temperature.
Using the stock suspension, conduct serial 1:10 dilutions in the 7 tubes ensuring dilution uniformity.
Use sterile, total outflow, disposable, glass 1-mL pipettes. Change pipette for each dilution.

Petri dish inoculation

Transfer 1 mL of homogenized suspension from the 7th tube to each of 3 sterile Petri dishes. Then plate the dishes with about 20 mL of molten culture medium. Swirl gently to mix the sample and the agar medium.

Incubation

When the 3 Petri dishes have cooled and the agar has solidified, invert the dishes and incubate at 30°C for 72 hours.

Colony count

After incubation, count the colonies of yeast in each dish using an automatic colony counter of the PROTOS type.

The result R is calculated as follows:

$$R = \frac{N \times 10^{T} \times (V + TS)}{TS}$$ = number of yeast cells /g of product under test (expressed as 10^9)

Where :

TS: the mass of the actual test sample (g)
V: diluent volume (mL)
T: No. of the last tube of dilution used
N: mean of the results, n_1, n_2, n_3, with $30 \leq n \leq 300$

- *Standard :*

The number of viable yeast cells is required to be not less than 18 billion per gram of lyophilized *Saccharomyces boulardii.*

c - Sulphated ash

The sulphated ash value for lyophilized *Saccharomyces boulardii* is determined as indicated in section 2.4.14. of the European Pharmacopoeia on an accurately weighed test sample of about 1 g.

Standard : the sulphated ash is required to be not more than 7%.

d - Control of microbial contamination

The control is conducted using methods close to that indicated in chapters 2.6.12. and 2.6.13. of the European Pharmacopoeia.

Sample preparation

Prepare a suspension of 10 g of lyophilized *Saccharomyces boulardii* in peptone buffer solution with sodium chloride, pH 7.0, so as to obtain 100 mL of suspension.

Total viable aerobic microorganism count

- Mesophilic bacteria

Transfer 1 mL of the sample prepared for assay and 15 to 20 mL of casein and soybean digest agar with actidione (Medium 2) to Petri dishes of diameter 90 mm.
Incubate at 30-35°C for 5 days.
Count the colonies that have grown.

Medium 2 - Casein soybean digest agar with actidione :
agar medium B

Pancreatic digest of casein	.....	*15.0 g*
Papaic digest of soybean	.....	*5.0 g*
Sodium chloride	.....	*5.0 g*
Agar	.....	*15.0 g*
Purified water	..... *qs*	*1000 mL*

Adjust the pH after sterilization in an autoclave to 7.3 ± 0.2. Sterilize by heating in an autoclave at 121°C for 15 minutes. At the time of use, add 0.5 mL of 0.4% actidione solution under sterile conditions.

Let n be the number of colonies counted. The number, N, of viable aerobic microorganisms in 1 g of lyophilized *Saccharomyces boulardii* is given by the formula :

$$N = n \times 10$$

Standard : N is required to be not more than 1000 CFU/g.

- Molds and other yeasts

Transfer 2 mL of the sample prepared for the assay and 15 to 20 mL of Sabouraud agar with chloramphenicol and actidione (medium 3 – See above) to 5 Petri dishes of diameter 90 mm.
Incubate at 20-25°C for 5 days.
Count the colonies which have grown.

Let n be the number of colonies counted. The number, N, of molds and other yeasts in 1 g of lyophilized *Saccharomyces boulardii* is given by the formula :

$$N = n \times 10$$

Standard : zero colonies.

Note : the addition of actidione to media 2 and 3 is necessary in order to inhibit the growth of the yeast, *Saccharomyces boulardii*, the active substance. The test thus enables counting yeasts other than *Saccharomyces boulardii*.

Testing for specified microorganisms

The tests are conducted as per method 2.6.13. of the European Pharmacopoeia, current Edition: 'Microbiological control of products not required to comply with the test for sterility' (test for specified microorganisms). Medium D is described hereafter (medium 4).

Medium 4 - Lactose broth medium (Medium D)

Nutrient broth with lactose		*32.50 g*
Sodium dihydrogen phosphate (NaH_2PO_4, 2 H_2O)		*13.25 g*
Disodium hydrogen phosphate (Na_2HPO_4, H_2O)		*29.25 g*
Purified water	*qs*	*2500 mL*

- *Enterobacteriaceae* and certain other Gram-negative bacteria
- *Escherichia coli*
- *Salmonella*
- *Pseudomonas aeruginosa*
- *Staphylococcus aureus*

Standard : zero colonies.

2. LIST OF ALL COUNTRIES WHERE THE CONDITION IS MARKETED

See Attachment 1 (page 53).

INFORMATION IN ACCORDANCE WITH PARAGRAPHS (C)(2)(I) THROUGH (C)(2)(V)OF 21 CFR 330.14 SUBPART B.

List of countries for which information will be submitted.
Given that the condition has been marketed in five or more counties for longer than five years the sponsor has selected seven countries for which detailed information is supplied.

2(I) HOW THE CONDITION HAS BEEN MARKETED

The condition has been marketed in compliance with national legislation that is equivalent[1] to OTC availability in 7 European countries for more than 10 years.

List of countries for which information in accordance with paragraphs (c)(2)(i) through (c)(2)(v)of 21 CFR 330.14 Subpart B is supplied :

Belgium

France

Germany

Italy

Portugal

Spain

Switzerland

[1] Please refer on page 14 : « Explanatory note regarding « OTC » status in countries selected for inclusion in this TEA »

Explanatory note regarding "OTC" status in countries selected for inclusion in the TEA for *S. boulardii.*

In the European countries specified above there is no pure "OTC" status as there is in USA. Even for drugs that are not under prescription control the involvement of pharmacist is generally needed.

Generally speaking, there are several levels of status :

- drugs on prescription only (not OTC status)
  these drugs are often taken in charge (totally or partially) by Social Security.

- drugs delivered with or without prescription
  (in France, some of these drugs are reimbursed when delivered on prescription)

- drugs delivered by pharmacies without prescription. In that case, in several countries, promotion can be made to consumers.

In the seven selected countries, the status of *S. boulardii* is "with or without prescription". The portion of *S. boulardii* sold without prescription can be considered as "OTC". In such instances, the proportions of drug sold OTC versus prescription cannot be precisely determined and so estimates have been made for the purpose of this TEA. Full details of the methodology used to make the estimates of OTC sale are provided on page 21.

The legal status of *S. boulardii* in these countries is not indicative that the Authorites have safety concerns that *S. boulardii* is inappropriate for OTC use.
If there were any such concerns that the drug could be inappropriate for OTC (direct purchase and consumption without physican involvement), then it would be placed in the "drugs on prescription only category". This is not the case in any of the countries.

General practitioners do have the freedom to prescribe the drug even if it is not mandatory because the drug is one of the drug of their Medical practice, sometimes for other indication than the one claimed for OTC use in this TEA. In some countries where the drug can be reimbursed by the national social security system, patients ask their doctors for a prescription, this being mandatory for reimbursement. Table 1 provides further details on marketing regulation in European countries selected for inclusion in the TEA.

TABLE 1 : Details on marketing regulation in European countries selected for inclusion in the TEA.

Country	**Drug sold in any general store**	**Sales of the drug restricted to pharmacies**	**Personal involvement of the pharmacist is required for delivering the drug**
BELGIUM	no	yes	yes
FRANCE	no	yes	yes
GERMANY	no	yes	yes
ITALY	no	yes	no
PORTUGAL	no	yes	yes
SPAIN	no	yes	yes
SWITZERLAND	no	no	no

Comments :

Country	Comment
FRANCE	The drug can be sold without prescription in Pharmacies a prescription is mandatory to customer to be reimbursed by Social Security. The drug being reimbursed by social security direct advertising to consumers is forbidden.
GERMANY	The drug can be sold without prescription in Pharmacies. Direct advertising to consumers can be done. The drug must be prescribed to be reimbursed by Social Security.

Country	Comment
ITALY	In Italy, there are 3 kinds of products : Class A and C : Prescription is mandatory. In A class the product is reimbursed in C class it is not. OTC drug : No need for prescription. Direct advertising to consumers is allowed. S.O.P. drug : No need for prescription. But direct advertising to consumers is not allowed. *S. boulardii* (tradename Codex) is S.O.P. drug. It is not reimbursed by Social Security.
SPAIN	In Spain, Medicinal products for human use are defined as « Ethical » and « EFP » Ethical : Distribution with or without medical prescription. Price approved from Health authorities Advertisement restricted to health care professionals EPF : Distribution without medical prescription. Company sets the price. Promotion can be done to public (after information of Health authorities) Both are sold exclusively in pharmacies *S. boulardii* (tradename Ultra-levura) is classified within ethical drugs.

Country	Comment
SWITZERLAND	In Switzerland, there are several category of drugs: A : sold against prescription in Pharmacies only with a strict control (for example : antibiotics) B : sold against prescription in Pharmacies C : OTC in pharmacies only D : OTC in pharmacies and drogeries. Drogeries are allowed to sell a limited assortment of registered health products (category D). In addition they sell cosmetics. Within drogeries, customers cannot have direct access to medicines themselves, medicines must be accessed via the sales staff. Drogeries are unique in Europe and they are not equivalent to US drugstores. *S. boulardii* is classified as D.

2(II) CUMULATIVE NUMBER OF DOSAGE UNITS SOLD AND ESTIMATE OF POTENTIAL CONSUMER EXPOSURE TO OTC SALES

Table 2 : See on following page 19

Pages 19-26 redacted

2(III) DESCRIPTION OF POPULATION DEMOGRAPHICS TO ENSURE THAT USE CAN BE EXTRAPOLATED TO U.S. POPULATION

Information relating to population demographics in the selected countries are provided in the following tables. The sponsor is not aware on any population demographic factors such as racial/ethnic group that impacts upon either the safety or efficacy of *S. boulardii*. This is supported by the comparison of demographic factors in the selected countries together with the supplementary information provided from additional countries in Attachment 4 (page 131).

DESCRIPTION OF THE POPULATION DEMOGRAPHICS

An extensive effort has been undertaken to obtain information on the percentage of various racial/ ethnic groups. All information obtained is tabulated below. Owing to the mechanism used to collect demographic information in the various countries, only very limited information on the percentage of various racial/ ethnic groups is obtainable. Generally information is collected in terms of 'country of origin' rather than by using definitions of racial or ethnic group.

Sources Providing Information for Individual Countries

The following information sources have been identified that provide racial/ethnic demographic information for individual countries.

Source of Information	Country: France
The National institute of statistics and economic studies (INSEE) (http://www.insee.fr/fr/home/home_page.asp) Census 1999, by nationalities	Country of origin as % of population French 90.4% Spanish 0.3%, Italian, 0.3%, Portugal, 0.9%, other EU (0.5%), Algerian, 0.8%, Moroccan, 0.9%, Tunisian, 0.3%, Turkish 0.4%. Other foreign 1.2%.

Source of Information	Country: Germany
Federal Statistical Office (http://www.destatis.de/e_home.htm) Last updated on 02 April 2003 http://www.destatis.de/basis/e/bevoe/bev_tab4.htm)	Citizenship 2001 as % of total population Germans 91.1%, foreign 8.8% incl.: - Turkey 2.4 - Yugoslavia (1) 0.8 - Italy 0.7 - Greece 0.4 - Bosnia and Herzegovina 0.2 - Poland 0.4 - Croatia 0.3 - Austria 0.2 - United States 0.1 - Macedonia 0.07 - Slovenia 0.02 (1) Serbia-Montenegro

Source of Information	Country: Italy
Source: National Institute of Statistics, Population & Demographic Statistics (http://demo.istat.it/e/) Foreigners resident in Italy. Resident population by sex and citizenship on 31st December 2000 (http://demo.istat.it/e/stra1/start.html)	Total (resident) population in Italy as of 1 January 2001 57,844,017 Total foreigners resident in Italy as of 31 Dec 2000 1,464,589 (2.6% of total resident population) Breakdown by country: see http://demo.istat.it/e/stra1/start.html

Source of Information	Country: Spain
2001 Census (http://www.ine.es/censo2001/index.html) Spanish National Institute of Statistics	Total population resident in Spain 2002 = 41.837.894 Foreigner's account for 2.14 % of population, including (as % total population) European 0.86%, American 0.48%, Asian o.o8% and African 0.15%. Detailed breakdown of country of origin of foreigners resident in Spain. http://www.ine.es/dacoin/dacoinci/migracion/exrexpn.xls

Source of Information	Country: Portugal
United Nations Economic Commission for Europe, Economic Analysis Division, Population Activity Unit, Fertility and Family Surveys http://www.unece.org/ead/pau/ffs/por/nt1.pdf	**Percent of population by nationality/ethnicity, 1990** Portuguese 98.4 Born abroad (total) 1.1 Europe 0.4 *Countries of EU - - - -* *0.4* *Others European countries - -* *0.0* Africa 0.4 America 0.3 Asia 0.0 Oceania 0.0 More than one nationality / Without nationality 0.5

Source of Information	Country: Switzerland
Source: Statistik Schweiz (Swiss Federal Statistical Office)(http://www.statistik.admin.ch/eindex.htm) http://www.statistik.admin.ch/stat_ch/ber01/eufr01.htm	**Permanent resident population by national origin 2001** Not including seasonal workers (25,460), persons with a short-term residents permit (20,267) and asylum seekers 65,790; incl. persons admitted provisionally)

Nationality	**absolute**	**%**
Total	7,261,210	100.0
Swiss	5,803,408	79.9
Foreigners	1,457,802	20.1

Nationality of permanent foreigners	**absolute n**	**% n**
Total	1,457,802	100.0
Italy	316,041	21.7
Ex-Yugoslavia	352,044	24.1
Portugal	136,246	9.3
Germany	117, 664	8.1
Spain	81, 832	5.6
Turkey	80,158	5.5
France	63,338	4.3
Rest of Europe	131,458	9 .0
Asia	81,731	5.6
America	53,404	3.7
Africa	40,442	2.8
Australia, Oceania	3,186	0.2
Stateless	258	0.0

Sources Providing Information for Several Countries

The following information sources have been identified that provide racial/ ethnic demographic information for several countries. Where available, the data for the U.S.A from these sources is included below for comparative information.

Source of Information	Country Information							
	U.S.A.	France	Germany	Italy	Spain	Portugal	Belgium	Switzerland
U.S. State Department: country background notes http://www.state.gov/r/pa/ei/bgn/	Data not presented	Ethnic groups: Celtic and Latin with Teutonic, Slavic, North African, Sub-Saharan African, Indochinese, and Basque minorities. Religion: Roman Catholic 90% (updated 2/03).	Population (2001 est.): 83 million. Ethnic groups: Primarily German; Danish minority in the north, Sorbian (Slavic) minority in the east; 7.3 million foreign residents (updated 5/02).	Primarily Italian, but there are small groups of German-, French-, Slovene-, and Albanian-Italians (updated 6/03.	Ethnic groups: Distinct ethnic groups within Spain include the Basques, Catalans, and Galicians (updated 6/02).	Ethnic groups: Homogeneous Mediterranean stock with small black African and Eastern European minorities (updated 8/02).	Data not presented (updated 7/02).	Mixed European (updated 3/02).

Source of Information	Country Information							
	U.S.A.	France	Germany	Italy	Spain	Portugal	Belgium	Switzerland
The CIA World Fact Book 2002 http://www.cia.gov/cia/publications/factbook/fields/2075.html This entry provides a rank ordering of ethnic groups starting with the largest and normally includes the percent of total population.	white 77.1%, black 12.9%, Asian 4.2%, Amerindian and Alaska native 1.5%, native Hawaiian and other Pacific islander 0.3%, other 4% (2000)	Celtic and Latin with Teutonic, Slavic, North African, Indochinese, Basque minorities	German 91.5%, Turkish 2.4%, other 6.1% (made up largely of Serbo-Croatian, Italian, Russian, Greek, Polish, Spanish)	Italian (includes small clusters of German-, French-, and Slovene-Italians in the north and Albanian-Italians and Greek-Italians in the south)	composite of Mediterranean and Nordic types	homogeneous Mediterranean stock; citizens of black African descent who immigrated to mainland during decolonisation number less than 100,000	Fleming 58%, Walloon 31%, mixed or other 11%	German 65%, French 18%, Italian 10%, Romansch 1%, other 6%

Source of Information	Country Information				
	U.S.A.	France	Germany	Italy	Spain
Council of Europe. Population Demographic Year Book , "Social Cohesion and Quality of Life", 2001 edition – http://www.coe.int/t/e/social_cohesion/population/demographic_year_book/2001_Edition/	No available	In March 1999 immigrants accounted for 7.4 % of the population of mainland France. The proportion of immigrants from European countries was 45 % in 1999. Immigrants from other regions (as % of total immigrant population) come mainly from sub-Saharan Africa (37 %), Asia (35 %) and Turkey (16 %).	Not available	The foreign population resident in Italy accounted for 2.2 % total resident population (according to population data in the municipal registers for 1999). Of the total number of foreigners living in Italy at the end of 1998, 38,4 % were Europeans of which 24.2 % came from Central and Eastern Europe; 32.8 % from Africa of which 21.6 % came from North Africa; 18.7 % from Asia and 9.8 % from the Americas.	The percentage of foreign residents in Spain has increased notably from about 0.5 % of the total population in 1980 to 1.1 % at the end of 1990, and reached 2.2 % at the end of 2000. No demographic breakdown available.

Source of Information	Country Information			
	U.S.A.	Portugal	Belgium	Switzerland
Council of Europe. Population Demographic Year Book , "Social Cohesion and Quality of LIfe", 2001 edition – http://www.coe.int/t/e/social_cohesion/population/demographic_year_book/2001_Edition/	Not available	According to the data provided by the Ministry of the Interior, the resident foreign population in Portugal in 1999, was 190 896 (178 137 in 1998, revised data) or 1.91 % of the total population.. Most of the immigrants come from Africa (46.9 % in 1999 against 42.1 % in 1991). The number of immigrants from Cape Verde has decreased (from 26.1 % in 1991 to 22.9 % in 1999), whereas the proportion of people coming from Angola and Guinea-Bissau has increased from 5 % to 9.3 % and from 4.2 % to 7.4 % respectively over the same period. In 1999 29.7 % of the foreign residents in Portugal were Europeans (29.2 % in 1991). Most of the European immigrants come from United Kingdom (7.0 %), Spain (5.8 %) and Germany (5.0 %). The proportion of Brazilian residents remained stable between 1991 and 1999 (10.9%).	1st January 2001 Belgians 9401729 (91.6%) Foreigners 861685 (8.4%) Total 10 263 414 As at 1 January 2001, the largest numbers of foreigners came from the following countries: Italy, 195 586 (22.7 %); France, 109 322 (12.7 %); Morocco, 106 822 (12.4 %); Netherlands, 88 813 (10.3 %); Turkey, 56 172 (6.5 %); Spain, 45 356 (5.3 %); Germany, 34 579 (4.0 %); United Kingdom, 26 600 (3.1 %); and Portugal, 25 634 (3.0 %). Together these countries accounted for 80.0 % of all foreigners.	In 2000 1.656% of resident population were foreign, including people holding annual residence permits, seasonal workers and asylum-seekers. No percentage demographic figures are available.

Source of Information	Country Information							
	U.S.A.	France	Germany	Italy	Spain	Portugal	Belgium	Switzerland
InfoPlease Almanac: Ethnicity and Race by Countries. Accessed May 22, 2003 http://www.infoplease.com/ipa/A0855617.html	White: 211,460,626 (75.1%); Black: 34,658,190 (12.3%); American Indian and Alaska Native: 2,475,956 (0.9%); Asian: 10,242,998 (3.6%); Native Hawaiian and Other Pacific Islander: 398,835 (0.1%); Other race: 15,359,073 (5.5%); Hispanic origin: 35,305,818 (12.5%)	Celtic and Latin with Teutonic, Slavic, North African, Southeast Asian, and Basque minorities. No percentage provided.	German 91.5%, Turkish 2.4%, Italians 0.7%, Greeks 0.4%, Poles 0.4%, other 4.6%	Italian (includes small clusters of German-, French-, and Slovene-Italians in the north and Albanian-Italians and Greek-Italians in the south), Sicilians, Sardinians. No percentages provided.	Composite of Mediterranean and Nordic types. No percentages available.	Homogeneous Mediterranean stock in mainland, Azores, Madeira Islands; citizens of black African descent who immigrated to mainland during decolonisation number less than 100,000	Fleming 55%, Walloon 33%, mixed or other 12%	German 65%, French 18%, Italian 10%, Romansch 1%, other 6%

Source of Information	Country Information							
	U.S.A.	France	Germany	Italy	Spain	Portugal	Belgium	Switzerland
Source: Yahoo World Fact Book (http://education.yahoo.com/reference/factbook/po/popula.html)	white 83.5%, black 12.4%, Asian 3.3%, Amerindian 0.8% (1992)	Celtic and Latin with Teutonic, Slavic, North African, Indochinese, Basque minorities	German 91.5%, Turkish 2.4%, other 6.1% (made up largely of Serbo-Croatian, Italian, Russian, Greek, Polish, Spanish)	Italian (includes small clusters of German-, French-, and Slovene-Italians in the north and Albanian-Italians and Greek-Italians in the south)	Composite of Mediterranean and Nordic types	Total Population **10,048,232** (July 2000 est.) Ethnic groups: homogeneous Mediterranean stock; citizens of black African descent who immigrated to mainland during decolonisation number less than 100,000 (1.0 %)	Fleming 58%, Walloon 31%, mixed or other 11%	German 65%, French 18%, Italian 10%, Romansch 1%, other 6%

2(IV) DIFFERENCES IN PATTERN OF USE

TABLE 4 : Pattern of Use : Current Approved OTC / Prescription Dose and Duration

Country	Dosage	Daily dose		How often the drug is to be used in the day	Duration of treatment
		Number of capsules	mg / day		
BELGIUM	50 mg	(1) (2)	300 - 400	(1)	(1)
FRANCE	50 mg	4 capsules	200	bid	(1)
GERMANY	50 mg	6 - 12 capsules	300 – 600	tid	Treatment should continue for a few days after the diarrhea has stopped
	250 mg	1 - 2 capsules	250 - 500	1 or 2 times a day	Treatment should continue for a few days after the diarrhea has stopped
ITALY	250 mg	2 to 4 capsules	500 - 1000	bid	(1)
PORTUGAL	250 mg	1 - 3 capsules	250 – 750	from one to 3 times per day	(3)
SPAIN	50 mg	initial treatment: 6 to 8 capsules maintenance treatment: 2 capsules	300 – 400 100	Bid .	(1)

(1) This information is not specified in the approved leaflet.

(2) In the approved information to doctor daily dose is: Prevention 3 capsules bid ; Treatment 4 capsules bid.

(3) "The duration of treatment must be decided by the treating doctor, on the basis of the individual patient's response and the severity of the symptoms."

TABLE 4 : Pattern of Use : Current Approved OTC / Prescription Dose and Duration (continued)

Country	Dosage	Daily dose		How often the drug is to be used in the day	Duration of treatment
		Number of capsules	mg / day		
SWITZERLAND	50 mg	initial treatment: 10 capsules	500	(1)	(1)
		chronic infections maintenance treatment: 4 capsules	200		
		prevention: 2 to 4 capsules	100 – 200		
	250 mg	initial treatment: 2 capsules	250 – 500	Bid	(1)
		maintenance treatment: 1 capsule	250		

In comparison, the proposal for OTC approval in the U.S. is as follows :

Country	Dosage	Daily dose		How often the drug is to be used in the day	Duration of treatment
		Number of capsules	mg / day		
USA	250 mg	1 - 2 capsules	250 – 500	1 or 2 times a day	Treatment should be continued until the symptoms of diarrhea have resolved. If no improvement is seen within two days, doctor must be consulted

(1) This information is not specified in the approved leaflet.

Note :

- In some countries a 50 mg capsule is marketed (Belgium, France, Spain) in two other countries 50 mg and 250 mg capsules are marketed (Germany, Switzerland) and in two other countries only 250 mg capsules are marketed (Italy, Portugal).

There is no resorption of the active ingredient which is the living yeast cells of *Saccharomyces boulardii. Saccharomyces boulardii* acts within the intestinal tract where it passes through, exerting its biological effects thus, we consider that 5 x 50 mg of *Saccharomyces boulardii* are therapeutically equivalent to 1 x 250 mg. In this TEA, calculation of the number of potential consumer exposures is possible for the 50 mg and 250 mg capsule strengths. Since the 50 mg and 250 mg capsules are approved at comparable daily doses, all time and extent data from both capsule strengths is considered valid in supporting the proposed TEA.

Explanatory comments regarding differences in pattern of use across countries :

There are differences from one country to another but globally daily doses are typically in the range of 250 to 500 mg i.e. a dose comparable to that proposed for U.S. OTC approval. The national differences in dosages approved result from different licensing decisions that have arisen by independent national European Regulatory Authorities. The dosage proposed for OTC use in the U.S. is consistent with the dosage range approved globally.

- Different capsule strengths i.e. 50 or 250 mg are marketed in different countries dependant upon local marketing strategy and preferences.

- The drug is usually taken twice a day.

- Duration of treatment is not precised on leaflets except for Germany where it is specified that treatment should continue for a few days (we recommend for 2 days) after the diarrhea has stopped

2(v) Countries System for Identifying Adverse Experiences. Particularly Those Which Occur in an OTC Setting

Belgium

As a member of the European Union, Belgium must comply with all relevant European legislation relating to pharmacovigilance. All Member States must have established systems for pharmacovigilance and mechanisms for addressing safety issues

Belgium has a centralised system of pharmacovigilance. The Belgian Centre for Pharmacovigilance within the Ministry of Health is responsible for the collection and evaluation of reports of adverse drug reactions and for follow-up communication with healthcare professionals.

Healthcare professionals submit adverse drug reaction reports. These are sent to the regional centre or Marketing Authorisation Holder (MAH) using a yellow card system. For OTC products reporting of adverse drug reactions is by pharmacists or physicians. The MAH submits reports to the Belgian centre for Pharmacovigilance on a CIOMS form, while doctors and other health professionals use a yellow card system. If serious, suspected adverse reactions are reported within 15 days.

France

As a member of the European Union, France complies with all relevant European legislation relating to pharmacovigilance.

The french system is on 3 levels :

- watch is kept by all health care professionals, who are under legal obligation to report adverse effects of medicines available on the market ;
- the second level consists of 31 regional drug safety monitoring centres distributed throughout France in main university hospital groups.This regional distribution enhances exchanges in the field between health care professionals. The role of these regional centres is to valide information and carry out enquiries ;
- the system is then centralised at the Agence Française de Sécurité Sanitaire des Produits de Santé / French Agency for the Safety of Health Products (AFSSaPS), the Commission Nationale de Pharmacovigilance / National Drug Safety Monitoring Commission and its Comité Technique de Pharmacovigilance / Drug Safety Monitoring Technical Committee.

The possibility of a causal relationship between taking the medicine and the adverse effect undergoes an analysis known as a causality (imputability) assessment which uses a technique shared by all centres and the drug safety monitoring units of pharmaceutical companies. This method has been made official by Decree and published in the Bulletin Officiel / Government Gazette. This French method for evaluation of the causality of unexpected or toxic effects of medicines combines clinical and laboratory information necessary for causality evaluation (chronology of events, description of adverse effect, result of appropriate laboratory investigations).

The company distributing a medicine must inform the AFSSaPS of any serious adverse effect potentially attributable to that medicine.

Regional drug safety monitoring centres must send on without delay information concerning serious adverse events they receive from hospitals and other health care facilities.

The AFSSaPS informs the EMEA within fifteen days at the latest after having been notified of a serious adverse event.

The company also sends the AFSSaPS a periodic report summarising information concerning all adverse effects :

- immediately, on request ;
- every six months during the two years after the MA is granted ;
- annually for the next three years, then every five years.

This organisation applies also for OTC products. In that case, pharmacists are more frequently involved. They report either to regional drug safety monitoring or directly to the company.

Germany

As a member of the European Union, Germany must comply with all relevant European legislation relating to pharmacovigilance. All Member States must have established systems for pharmacovigilance and mechanisms for addressing safety issues

Germany has a centralized system of pharmacovigilance. The marketing authorization holder has to notify all serious drug effects, all serious interactions as well as all misuses to the German Regulatory Authority the BfArM (Bundesinstitut für Arzneimittel und Medizinprodukte) within 15 days of receipt.

Germany requires the filing of a safety report according to a distinct German format known as *Erfahrungsbericht* (experience report), in addition to the European PSUR. This is required by the German Medicines 02/93, Act §49, paragraph 6, Drug Law (AMG), and has different data time locks (linked to the German birth date) compared to the EU PSUR. The marketing authorization holder has to collect all reported drug effects or interactions and report them to the authority every 6 months for two years and then annually for the three following years after initial marketing authorization or immediately upon request. Afterwards he has to submit a summary every 5 years or immediately upon request.

Serious drug effects reports from Germany, including spontaneous, clinical trial and literature, should be reported in German, preferably on the old BfArM form (BfArM 643). Foreign reports can be provided in English on a CIOMS I form.

In the case of OTC products reporting is via pharmacists or physicians.

According to the Medical and Pharmaceutical Association's professional code of conduct the physicians and the pharmacists have to report all observed drug effects to the pharmaceutical commission of these associations. The pharmaceutical commissions submit the reported drug effects to the authority.

Italy

As a member of the European Union, Italy must comply with all relevant European legislation relating to pharmacovigilance. All Member States must have established systems for pharmacovigilance and mechanisms for addressing safety issues.

As of 18th May 2003 new pharmacovigilance reporting procedures were established in Italy. The new procedure maintains the decentralised network of local Pharmacovigilance Units within Italy. Overall responsibility for coordination of pharmacovigilance system and issues is held by the Italian Ministry of Health (MoH).

The Marketing Authorisation Holder (MAH) must record in a specific file all the suspected ADR observed in Italy, EU or a third Country. The MAH must record and notify within< 15 days, all the suspected serious ADR, received from Health Personnel, to the local Pharmacovigilance Unit or to the MoH if the local Pharmacovigilance Unit is not operative. The MAH must record and notify within< 15 days, all the suspected serious ADR, to the MoH. Additionally, the MAH must record and notify within< 15 days, all the suspected unexpected serious ADR (SUSAR), received from Health Personnel of a foreign country, to the MoH

The MAH must provide a Period Safety Update Report to the MoH according to the timelines due following the international date of MA in compliance with relevant EU legislation.

Health Personnel must notify all the suspected serious ADR or unexpected ADR, to the local Pharmacovigilance Unit. In the case of OTC medicines reporting is via Pharmacists or Physician. Health Personnel should use the appropriate *Form (same format of CIOM-I)* to notify the local Pharmacovigilance Unit. The responsible of the local Pharmacovigilance Unit should insert the notified ADR into the National Web of pharmacovigilance within 7 days. The Italian MoH will assure that the MAH will be informed about all the suspected serious ADR within 15 days

Portugal

As a member of the European Union, Portugal must comply with all relevant European legislation relating to pharmacovigilance. All Member States must have established systems for pharmacovigilance and mechanisms for addressing safety issues

INFARMED (Portuguese Health Authority) is the responsible entity for the accompanying, coordination and application of the National Pharmacovigilance System and is the interface with the international Organizations/ Agencies.

The national pharmacovigilance system is constituted by the National Pharmacovigilance Centre (CNF) (INFARMED department responsible for pharmacovigilance activitics), by 4 pharmacovigilance units organised per geographic region, by health-care professionals, health services and marketing authorisation holders.

The pharmacovigilance units may be involved in the receipt, classification and validation of ADR information as well as additional follow-up information. Nevertheless, ADR initial and follow-up information processing as well as dissemination of safety information (Newsletters, Bulletins, and Alerts...) to the health care professionals and marketing authorisation holders is responsibility of the National Pharmacovigilance Centre (CNF).

Adverse events/ adverse drug reactions are submitted through the yellow, purple and white card systems for physicians, pharmacists and nurses respectively.

The MAH must have in place a pharmacovigilance system and is obliged to notify the National agency of AE/ADR information. These AE/ADR reports must be submitted to the CNF on a CIOMS form and whenever they are serious (expected or unexpected) must be notified to the CNF within 15 consecutive days. Non-serious AE/ADR information should be provided in the periodic safety update reports according to the timelines established.

In the case of OTC products, the role of the pharmacists is usually more empathised, since physicians may not have access to the AE/ADR information. The notification procedures are the same as for any other prescribed medicinal product.

Spain

As a member of the European Union, Spain must comply with all relevant European legislation relating to pharmacovigilance. All Member States must have established systems for pharmacovigilance and mechanisms for addressing safety issues

Spain has a decentralised pharmacovigilance system, with 15 regional pharmacovigilance centres. The National Commission on Pharmacovigilance reports to the Ministry of Health on drug safety issues. This Commission meets three times a year. Within the agency there is a co-ordinating centre for pharmacovigilance (Division of Pharmaco-epidemiology and Pharmacovigilance, Madrid). The co-ordinating centre for pharmacovigilance is connected online with the 15 regional centres to the ADR database (FEDRA) where information is entered after individual evaluation of the reports. Different types of queries can be performed in real-time and the data obtained are managed locally with a SAS program.

Healthcare professionals submit adverse drug reaction reports. These are sent to the regional centre or Marketing Authorisation Holder (MAH) using a yellow card system. For OTC products reporting of adverse drug reactions is by pharmacists or physicians.

The MAH submits reports to the co-ordinating centre on a CIOMS form, while health care professionals use the equivalent of the 'yellow card'. All information, irrespective of the pathway followed, is integrated into the FEDRA database.

Regional centres evaluate and process the reports they receive. They also interact with the reporter, sending reporting cards, informing of safety issues through periodic bulletins, and actively promoting ADR reporting. The co-ordinating centre manages reports from MAHs and issues all serious reports on a 15-day basis.

Switzerland

Switzerland has a decentralized pharmacovigilance system via which pharmacovigilance data from seven designated regional centres (five centered at major teaching hospitals), are collated independently and gathered for the Swiss Regulatory Agency, Swissmedic.

Any company manufacturing or distributing medicinal products must put in place a system of notification and is obliged to notify the Agency for undesirable effects or occurrences.

Any person professionally administering therapeutic products has to notify the Agency for all serious and previously unknown undesirable effects and occurrences or quality defects. Consumer, patients and organizations as well as interested third parties, may notify the Agency for undesirable effects of, and occurrences with, therapeutic products.

All serious adverse events have to be notified within 15 days to the regional pharmacovigilance centers using a specific notification form. In the case of OTC medicines reporting would be via the pharmacist or physician. Deaths or life-threatening undesirable effects should be notified as soon as possible. Previously unknown undesirable effects (not serious) should be notified within 60 days. The notification has to be made on a special notification form that has to be sent to the regional pharmacovigilance centers named on this notification form:

Within 7 days the regional pharmacovigilance centers confirm the receipt of this notification with a comment and forward it to Swissmedic. Swissmedic is responsible for the central undesirable effect database of Switzerland. They transfer all serious and previously unknown undesirable effects to the company as well as to the WHO Drug Monitoring Center (monthly).

Periodic Safety Update Reports have to be submitted every 6 months for two years and then annually for the three following years after marketing authorization.

3. HOW LONG CONDITION HAS BEEN MARKETED IN EACH COUNTRY. HOW LONG CURRENT LABELLING HAS BEEN APPROVED

TABLE 5 : Duration of Marketing ; Labelling

Country	How long condition has been marketed	How long current labelling has been in use	It has been authorized accepted or approved by a regulatory body
BELGIUM	41 years	more than 10 years	yes
FRANCE	41 years	2½ years (August 2000)	yes
GERMANY	20 years	3 years (February 2000)	yes
ITALY	10 years	3 years	yes
PORTUGAL	18 years	1 year (March 2002)	yes
SPAIN	11 years	11 years	yes
SWITZERLAND	39 years	10 years (Sept. 1993)	yes

Copies of relevant approved labelling and English translations are provided in Attachment 2.

4. RATIONALE FOR COUNTRIES SELECTED FOR PRESENTATION OF INFORMATION IN ACCORDANCE WITH PARAGRAPHS (C)(2)(I) THROUGH (C)(2)(V) OF 21 CFR 330.14 SUBPART B.

These European countries, 6 of which are part of EEC, have experienced more than 10 years marketing of the drug on a large scale of "OTC" sales and a great number of patients exposed to the drug.

They are all part of countries listed in section 802 (b)(1)(A) of the Federal Food, Drug and Cosmetic Act.

In order to further support extrapolation of information to the U.S. population we have added, in attachment 4, sales statistics in countries with specific racial / ethnic populations. While detailed estimates of numbers of consumers potentially exposed to *S. boulardii* OTC in these countries are not included in this TEA, the significant number of dosage units sold in these countries is indicative of the great extent of use of this drug.

Central and South America

Argentina
Brazil
Chile
Colombia
Mexico

Africa

Cameroun
Congo
Gabon
Ivory Cost
Morocco
South Africa
Senegal
Tunisia

Far East

Korea

Other

India
Pakistan

Except the countries from Central and South America (see next page) the drug is without prescription in all other countries listed above.

5. COUNTRIES WHERE THE CONDITION IS MARKETED ONLY AS A PRESCRIPTION DRUG.

Scandinavian countries (Finland, Denmark and Sweden) have registered the drug recently in non-OTC indications only i.e. :

- antibiotic associated diarrhea
- treatment of recurrent intestinal infections due to *Clostridium difficile* in addition to standard antibiotic therapy.

Thus these countries registered the drug as only a prescription drug in indications that are not appropriate for OTC use. This provides a clear rationale for limiting sale only to prescription use.

This was also the case in Turkey and Lithuania i.e. approval only in non-OTC indications. However, in Turkey sale is currently equivalent to OTC, irrespective of indication.

In Central and South America, Health Authorities, pushed by WHO strong opinion consider "diarrhea" as a major concern, want to limit self-medication and put the drug under the status of "prescription only". Practically, like in Turkey, the drug can be bought freely in pharmacies.

6. COUNTRIES WHERE THE CONDITION HAS BEEN WITHDRAWN FROM MARKETING OR IN WHICH AN APPLICATION FOR OTC MARKETING APPROVAL HAS BEEN DENIED.

S. boulardii has not been withdrawn from marketing in any country.

OTC Marketing approval has not been denied in any country.